

SUPPLEMENTAL MATERIAL to:

Intrinsic Human Elimination Half-Lives of Polychlorinated Biphenyls Derived from the Temporal Evolution of Cross-Sectional Biomonitoring Data from the UK Population

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Model equation

The population pharmacokinetic (PK) model applied in this publication is based on a multi-individual pharmacokinetic framework recently presented (Ritter et al. 2009). It describes concentration-time trends in a population based on multiple individuals representing different average birth-cohorts (Alcock et al. 2000, Pinsky and Lorber, 1998). The concentration-time trend in a population including all ages observed as a function of calendar time can be described by three temporal descriptors, i.e. the year of sampling t , the year of birth, t^{birth} and the age at the year of sampling, t^{age} . If two temporal descriptors are known, the third is given by eq. S1 (Ritter et al. 2009):

$$t = t^{\text{birth}} + t^{\text{age}} \quad \text{eq. S1}$$

Hence, the three temporal descriptors reflect two temporal dimensions. The differential equation describing the change in concentration in a single individual under the condition of a variable, age-dependent size of the lipid compartment can be derived from a single-individual first order mass-balance equation given in eq. S2 and the application of the quotient rule as in eq. S3:

$$\frac{dm(t^{\text{age}})}{dt} = m'(t^{\text{age}}) = -k_{\text{elim}} \cdot m(t^{\text{age}}) + I(t^{\text{age}}) \quad \text{eq. S2}$$

$$\frac{dC(t^{\text{age}})}{dt} = \frac{d(\frac{m(t^{\text{age}})}{M_{\text{lip}}(t^{\text{age}})})}{dt} = \frac{m'(t^{\text{age}}) \cdot M_{\text{lip}}(t^{\text{age}}) - m(t^{\text{age}}) \cdot M_{\text{lip}}'(t^{\text{age}})}{M_{\text{lip}}^2(t^{\text{age}})} \quad \text{eq. S3}$$

where $C(t^{\text{age}})$ is the concentration of a chemical in the human body under the assumption that the chemical is exclusively and homogenously distributed in the lipid compartment of the body, $m(t^{\text{age}})$ represents the mass of the chemical in the lipid compartment, $M_{\text{lip}}(t^{\text{age}})$ represents the size of the lipid compartment represented by units of lipid mass, $M_{\text{lip}}'(t^{\text{age}})$ is the derivative of $M_{\text{lip}}(t^{\text{age}})$ with respect to time, and $I(t^{\text{age}})$ is the daily intake of a chemical.

Inserting eq. S2 into eq. S3 leads to:

$$\frac{dC(t^{\text{age}})}{dt} = \frac{1}{M_{\text{lip}}^2(t^{\text{age}})} (-k_{\text{elim}} \cdot m(t^{\text{age}}) \cdot M_{\text{lip}}(t^{\text{age}}) + I(t^{\text{age}}) \cdot M_{\text{lip}}(t^{\text{age}}) - m(t^{\text{age}}) \cdot M_{\text{lip}}'(t^{\text{age}})) \quad \text{eq. S4}$$

Which simplifies to:

$$\frac{dC(t^{\text{age}})}{dt} = -(k_{\text{elim}} + \frac{M_{\text{lip}}'(t^{\text{age}})}{M_{\text{lip}}(t^{\text{age}})}) \cdot C(t^{\text{age}}) + \frac{I(t^{\text{age}})}{M_{\text{lip}}(t^{\text{age}})} \quad \text{eq. S5}$$

In the context of population pharmacokinetic modeling, one individual is characterized by a specific birth year, t^{birth} , which is expressed in eq. S6. This equation is analogous to Equation 2 in the main text.

$$\frac{dC(t^{\text{age}})}{dt} = -(k_{\text{elim}} + \frac{M_{\text{lip}}'(t^{\text{age}})}{M_{\text{lip}}(t^{\text{age}})}) \cdot C(t^{\text{age}}) + \frac{I(t^{\text{age}}, t^{\text{birth}} = \text{const.})}{M_{\text{lip}}(t^{\text{age}})} \quad \text{eq. S6}$$

$\frac{M_{\text{lip}}'(t^{\text{age}})}{M_{\text{lip}}(t^{\text{age}})}$ has units of rate constant (time⁻¹) reflecting elimination by growth dilution, which

is the ratio of the change in the body lipid mass and the body's total lipid mass. Since this ratio depends on age, the decline in concentration due to body growth is also age-dependent. k_{elim} is the intrinsic elimination rate constant representing metabolic and non-metabolic pathways and is assumed to be independent of age (Grandjean et al. 2008).

Initial concentrations and intake by breast feeding

For each representative individual in our model, the initial concentration at birth and the intake by breast feeding are both derived from the lipid-normalized concentrations in their mother. To determine these concentrations in the mothers, the model is evaluated in a pre-run under the assumption that individuals are born uncontaminated and are not breast fed. In this pre-run it is still possible to determine realistic concentrations in the mothers, which are assumed to be 25 years old at childbirth, because it has been shown that the large concentration differences between formula- and breast-fed individuals disappear not later than at the age of 20 years (Kreuzer et al. 1997; Verner et al. 2008).

Given the concentration of the 25 year old mothers over time, the intake by breast feeding can now be determined from the average amount of breast milk consumed per day, i.e. 700 ml (U.S. Environmental Protection Agency 1997), the average fat content of breast milk, i.e. about 2.5% (Rogan et al. 1987), and the lipid-based concentration in the mothers.

The concentration of a new born representative individual is set to be equal to the concentration in its mother.

Fitting constraints and stability offered by multiple age/concentration Cross-Sectional Data

The simplest approach to accounting for ongoing exposure relates an average concentration from a single cross-sectional data (CSD) set to a constant intake from a total diet study via a pharmacokinetic expression at steady state. This approach has been employed to estimate elimination kinetics of different persistent chemicals (Geyer et al. 2004; Ogura 2004; Shirai and Kissel 1996). Equation eq. S7 shows the model used by Geyer et al. (2004).

$$t_{1/2} = \frac{0.693 \cdot c_{ss} \cdot m_f}{DI \cdot f} \quad \text{eq. S7}$$

Where f is the fraction of dose absorbed from food, c_{ss} is the concentration in adult humans at steady state, and m_f is the average mass of fat in humans and DI the dietary intake. It is evident that with such an expression it is not possible to estimate exposure, i.e. DI , and elimination, i.e. $t_{1/2}$, solely from biomonitoring data, i.e. c_{ss} . In addition, an overestimated intake can directly be compensated for by a shorter half-life to still fit the averaged biomonitoring data, i.e. c_{ss} , and vice versa. Hence, the estimates for the elimination half-life, $t_{1/2}$, derived from this approach with no temporal dimension of concentration changes depends entirely on the availability, quality and compatibility of the two values for c_{ss} and DI . In addition, the steady-state assumption with a constant intake does usually not reflect actual

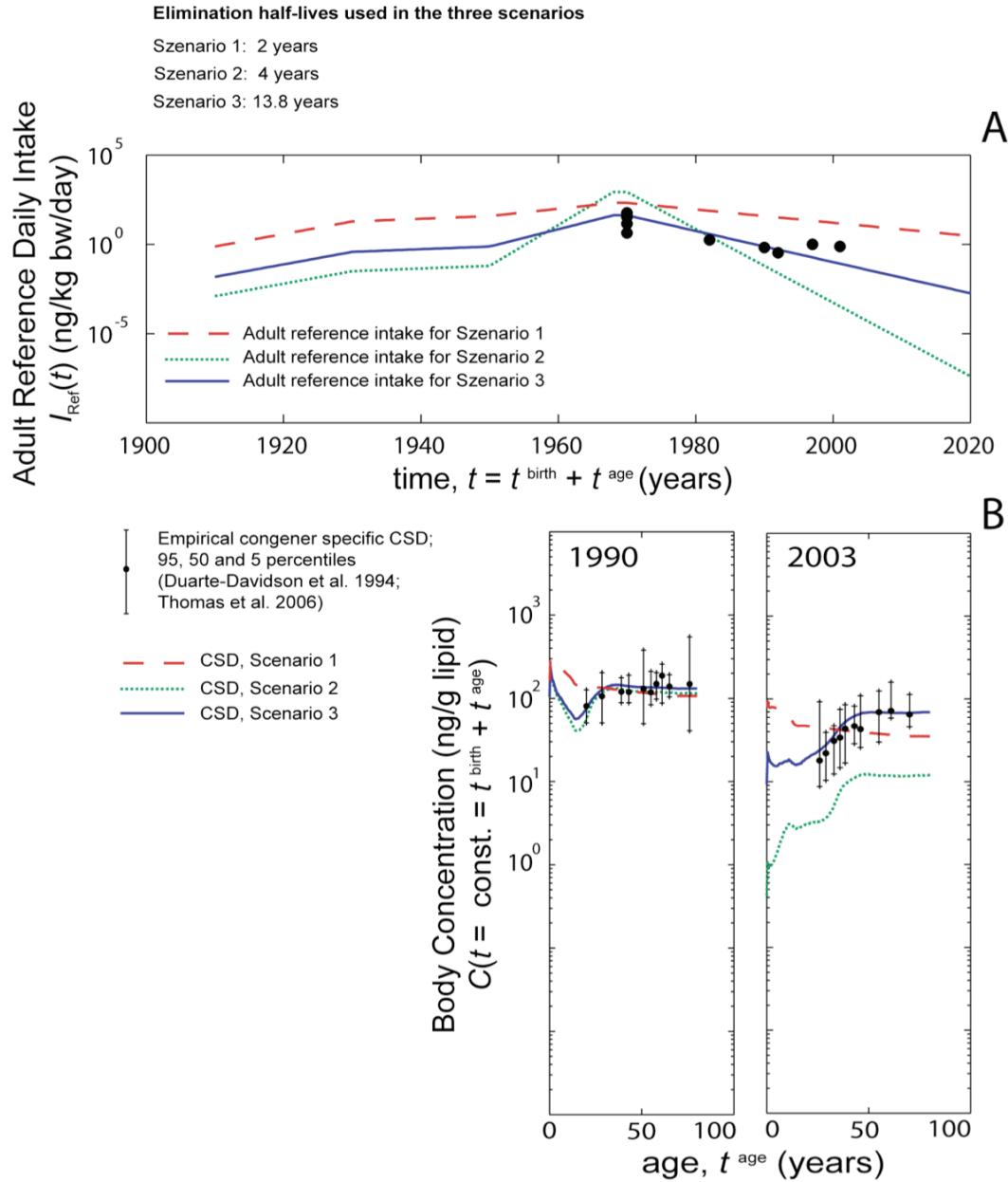
changing exposure trends and therefore leads to confounding effects especially for congeners with longer half-lives (Milbrath et al. 2009; Ogura 2004).

In difference, longitudinal data, cross-sectional trend data, and a single set of age/concentration CSD (see Table 1 in the main text) are biomonitoring data types that represent concentration changes along one temporal dimension. Although this constrains the possibility to fit the biomonitoring data more strongly than in the steady state approach, it is still possible to compensate for potentially incorrect exposure estimates by adjusting the target variable, i.e. the intrinsic elimination half-life. In other words, the relative contribution of exposure and elimination as determinants of concentration cannot unequivocally be quantified solely from these types of biomonitoring data with only one temporal dimension. Supplemental Material, Figure 1 illustrates this based on three hypothetical combinations of time trends in daily intakes, intrinsic elimination half-lives, and the age/concentration CSD of PCB153 at different points in calendar time.

Scenario 1 (high intake, elimination half-life of 2 years) represents the highest exposure-time trend, shown as a red dashed line in Supplemental Material, Figure 1A. Due to the short half-life of 2 years, which compensates for the high intake, the modeled age/concentration trends shown in Supplemental Material, Figure 1B pass through the “clouds” of both empirical cross-sectional data sets and approximately match their median concentrations. This reflects a good fit along the temporal dimension of calendar time, i.e. in both years of sampling, 1993 and 2000. However, from Supplemental Material, Figure 1B it becomes transparent that despite the fact that the combination of high intake with a short elimination half-life does fit median values of CSD well, there is no agreement concerning the relationship of concentration with age, the second temporal dimension. As a result, the optimization procedure described in the main text in such a situation would still lead to high values in the objective function and therefore to further variation of elimination and intake parameters by the least-square optimization algorithm.

Scenario 2 (dotted green line) with a slightly longer elimination half-life of 4 years and a more rapidly declining daily intake trend leads to a satisfying fit of age/concentration CSD sampled in 1990, but not in 2003. Hence, analogous to scenario 1, a good fit of modeled and empirical age/concentration CSD can be produced only along one temporal dimension, here age within the set of CSD from 1990, but not on the second temporal dimension, here represented by the year of sampling, i.e. the set of CSD sampled at a later point in time.

Scenario 3 (full blue line) shows the final result from the weighted least square optimization procedure as presented in the main text. Here, a good fit of modeled and empirical age/concentration CSD on both temporal dimensions is obtained with an intrinsic elimination half-life of 13.8 years and the estimated modeled empirical intake trend shown in Supplemental Material, Figure 1A as a blue line. This estimated modeled empirical intake trend is in good agreement with empirical intake data although this information was not included in the fitting process, which was in this case based on the objective function OF_{CSD_ONLY} .



Supplemental Material, Figure 1. Temporal dimensions in multiple age/concentration CSD as fitting constraints. This Figure illustrates how information of concentration changes along two temporal dimensions as contained in multiple age/concentrations CSD is distinctive in restricting the possible combinations of the model's parameterization for intake and elimination.

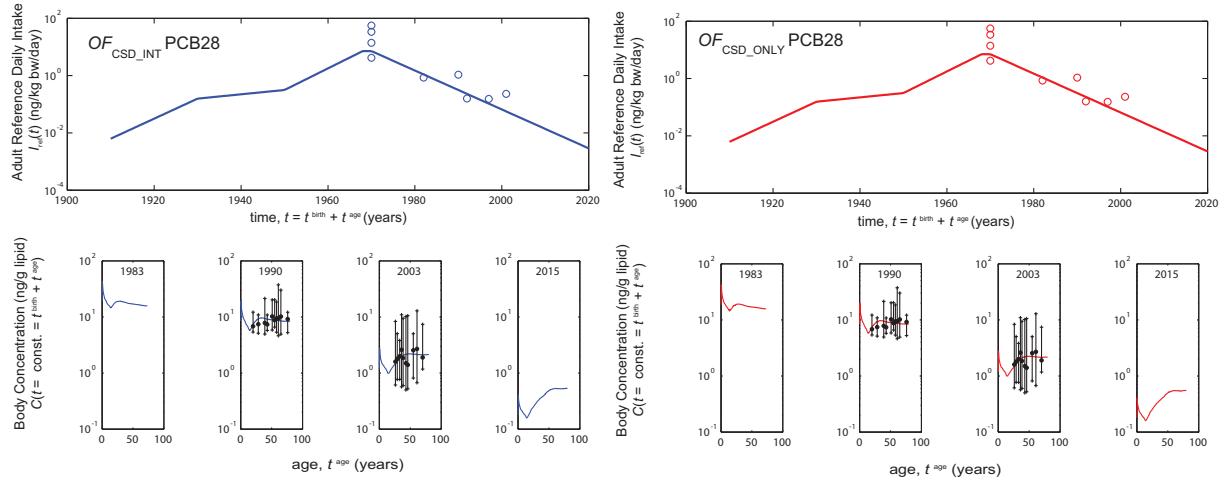
As described above, the availability of two dimensions, i.e. age and calendar time, offers considerably more fitting constraints as if only one dimension is available. For many congeners, the results obtained by fitting based solely on CSD, i.e. objective function $OF_{\text{CSD_ONLY}}$, is in good consistency with results obtained from the inclusion of empirical exposure data as an additional constraint, i.e. objective $OF_{\text{CSD_INT}}$ (Table 2, main text). In cases where a discrepancy between estimates based on $OF_{\text{CSD_INT}}$ and $OF_{\text{CSD_ONLY}}$ can be observed two explanations are possible: (i) there is an actual discrepancy between the exposure information obtained from the CSD sets compared to the information derived from the total diet studies or (ii) the fitting constraints based on only two sets of age/concentration CSD are not sufficient to obtain consistent results using $OF_{\text{CSD_INT}}$ and $OF_{\text{CSD_ONLY}}$. In the latter case, (ii), an additional CSD set may provide further constraints. Further research and

application of our approach by using more than two sets of age/concentration CSD and/or different representation of the model's exposure function, $I_{\text{ref}}(t)$, is needed to evaluate this issue. At this point, we recommend estimates based on $OF_{\text{CSD_INT}}$ since they reflect all empirical information available.

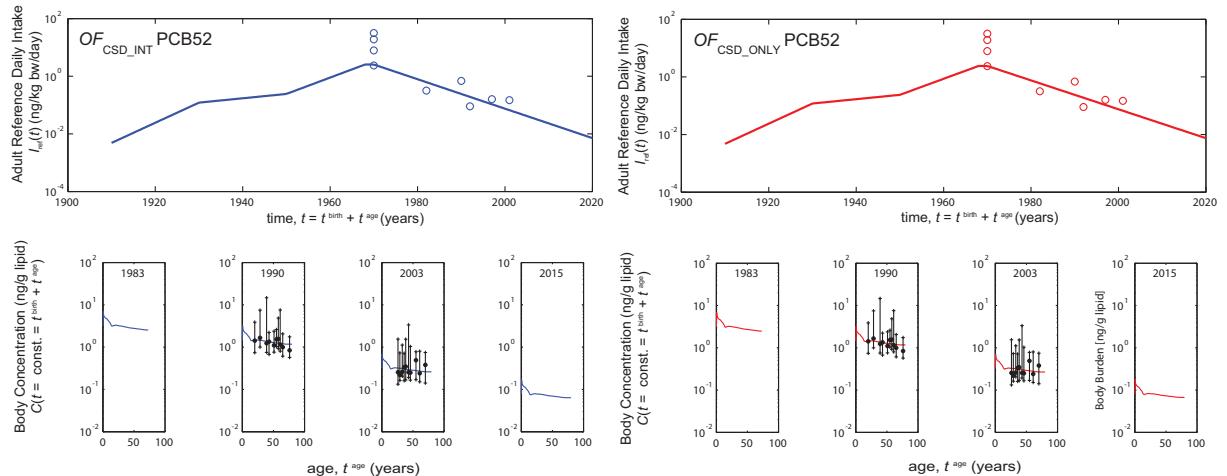
The fitting procedure was implemented in Software MATLAB (Mathworks 2010) and took about 48 hours for all 9 PCB congeners. For all 9 congeners, stability in the sense of reproducibility of results was tested and confirmed. Refitting the data led to half-lives maximally differing by a factor of 1.05.

Graphical results for all congeners

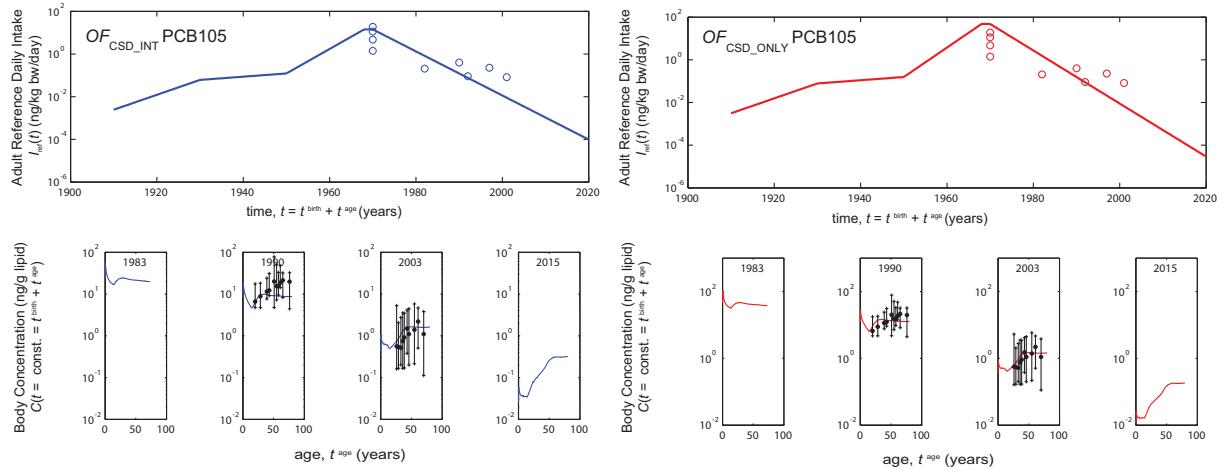
Supplemental Material, Figure S2 presents graphical results for all congeners. On the left-hand side modeled intakes and age/concentrations CSD based on $OF_{\text{CSD_INT}}$ are shown in blue. On the right-hand side modeled intakes and age/concentrations CSD based on $OF_{\text{CSD_ONLY}}$ are shown in red.



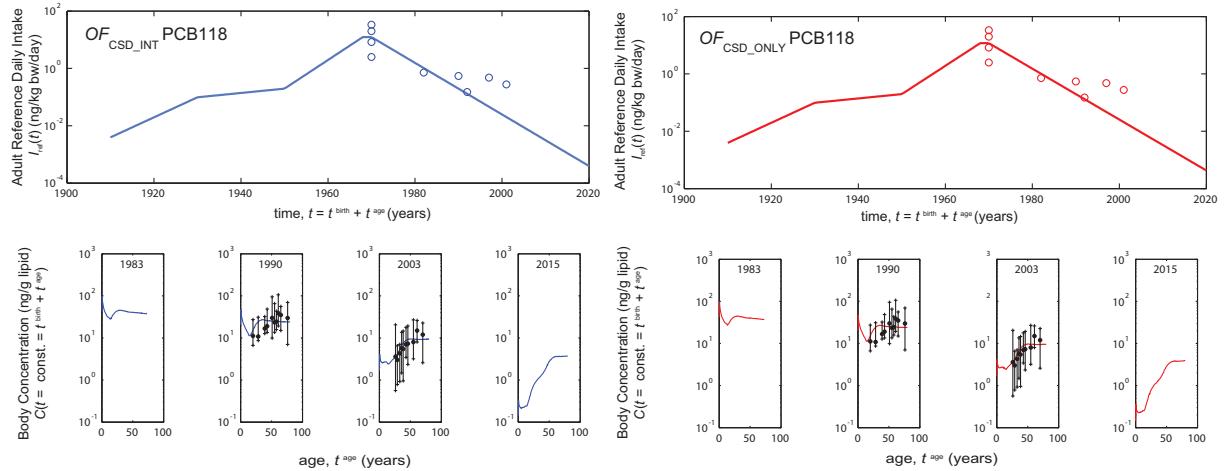
Supplemental Material, Figure 2a. Results for PCB28



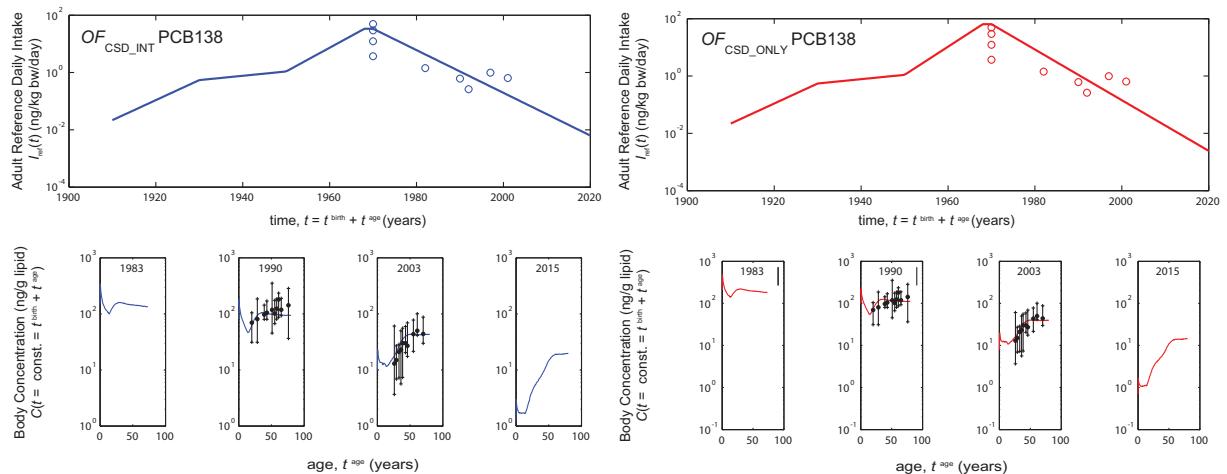
Supplemental Material, Figure 2b. Results for PCB52



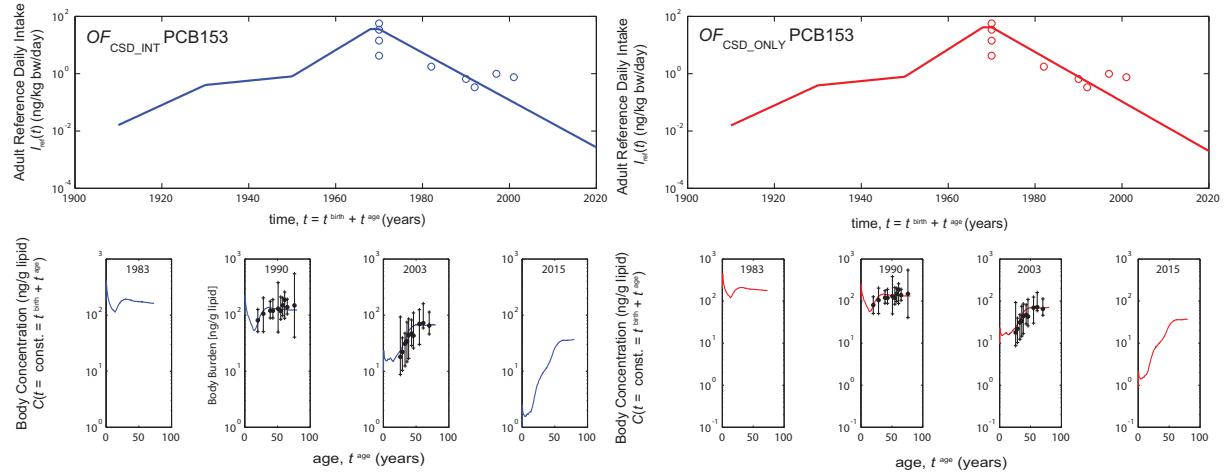
Supplemental Material, Figure 2c. Results for PCB105



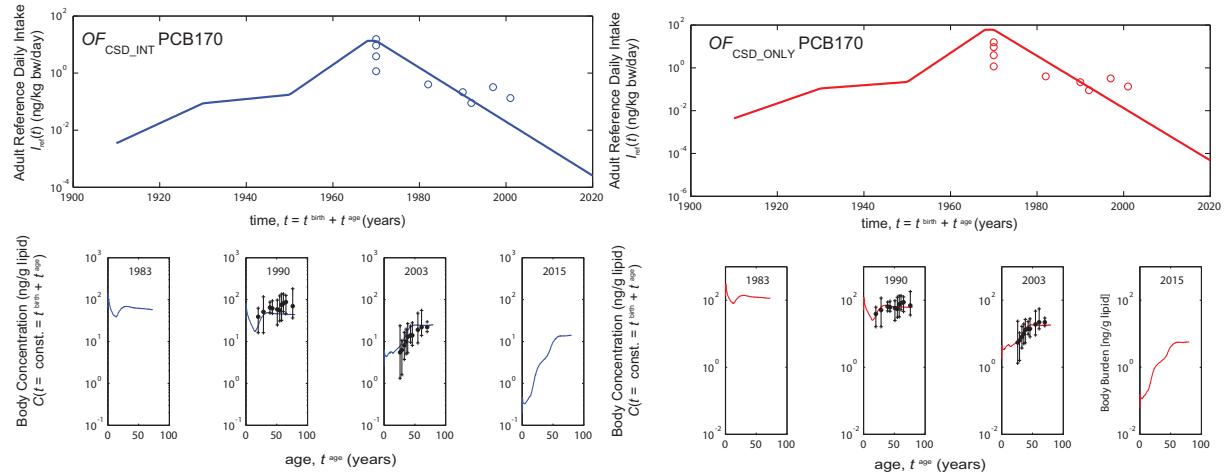
Supplemental Material, Figure 2d. Results for PCB118



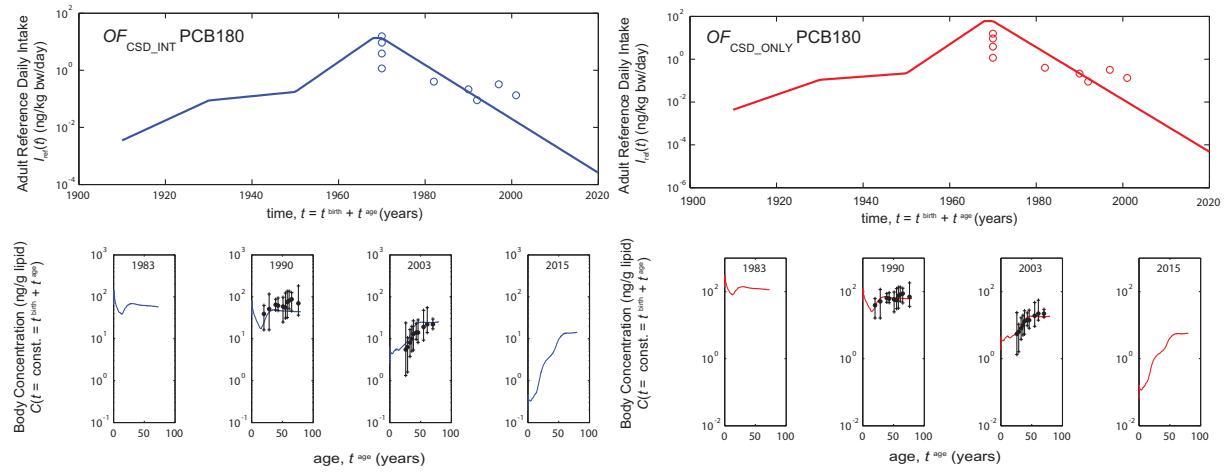
Supplemental Material, Figure 2e. Results for PCB138



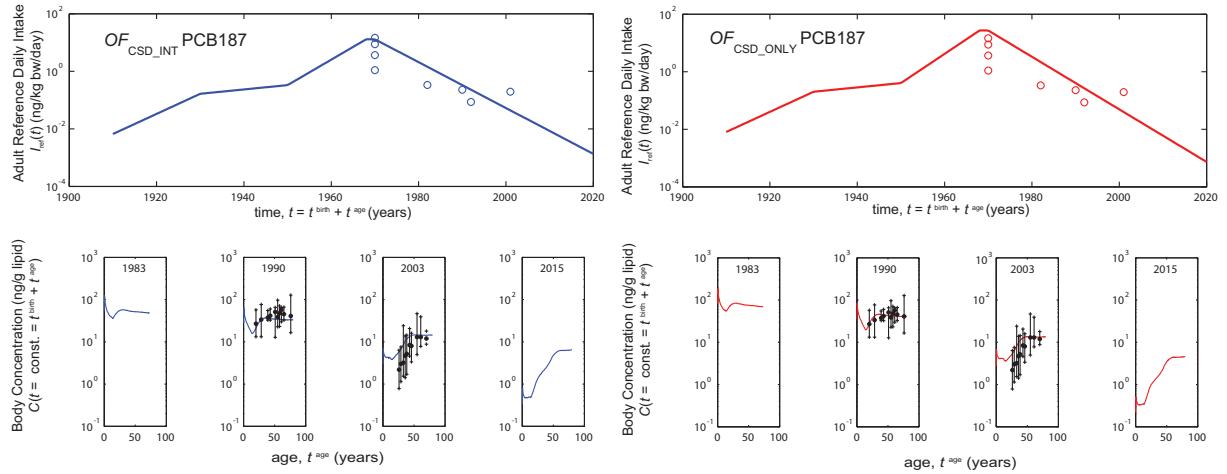
Supplemental Material, Figure 2f. Results for PCB153



Supplemental Material, Figure 2g. Results for PCB170



Supplemental Material, Figure 2h. Results for PCB180



Supplemental Material, Figure 2i. Results for PCB187

Empirical Adult Reference Daily Intake Data

Dietary intake is in most cases the major source of total human exposure to PCBs (Darnerud et al. 2006). Here we use empirical estimates of the adult reference daily intakes for the period 1982-2001 that are based on congener-specific measurements in food baskets from total diet studies (MAFF 1996; MAFF 1999; FSA 2003) that were multiplied by average UK food consumption data for the corresponding food basket. We used the same average food consumption data (Peattie et al. 1983) for the entire period 1982-2001, because the food basket categorization matched exactly the food basket categorization in all the total diet studies (MAFF 1996; MAFF 1999; FSA 2003). In addition, differences between consumption rates in 1986 and 2000 are relatively small (ONS 2002). For 1990, we used estimates of congener-specific dietary intakes for the UK population that were reported directly as daily intakes (Duarte-Davidson and Jones 1994), see Supplemental Material, Table 1.

No congener-specific daily intake data are available for 1970. We approximated congener-specific intake estimates for the year 1970 based on 4 values for \sum PCB intake that reflect the potential range of intake in 1970 reported in the literature: Duarte-Davidson and Jones (1994) (p. 146) report a daily intake of \sum PCB of 24 μ g/day for 1970 in a discussion of their own congener-specific estimates for 1990. This intake of \sum PCB of 24 μ g/day represents one of the four values of \sum PCB intakes used for the year 1970 (Supplemental Material, Table 1). The other three intake values for 1970, i.e. 40, 10 and 3 μ g/day of \sum PCB intake, represent the range of possible intakes as reported in MAFF (1983, p. 22). To approximate congener-specific intakes in 1970 from these four values of \sum PCB intake, we multiplied each of the four intakes of \sum PCB by the fraction that a specific congener contributed to \sum PCB intake in later studies. We used the median fractions from two congener-specific intake-studies from 1982 (MAFF 1996) and 1990 (Duarte-Davidson and Jones 1994). As a consequence of this approximation, estimates in 1970 are subject to higher uncertainty than those for later years.

Supplemental Material, Table 1: Estimates of congener specific daily adult reference intakes [ng/kg bw/day]²⁾ for PCBs

year	CB28	CB52	CB105	CB118	CB138	CB153	CB170	CB180	CB187	References
1970	55.9	31.6	18.8	33.3	49.2	56.8	15.5	30.9	14.6	extrapolation from \sum PCB intake (40 µg/day) ¹⁾
1970	33.5	19.0	11.3	20.0	29.5	34.1	9.3	18.5	8.8	extrapolation from \sum PCB intake (24 µg/day) ¹⁾
1970	14.0	7.9	4.7	8.3	12.3	14.2	3.9	7.7	3.7	extrapolation from \sum PCB intake (10 µg/day) ¹⁾
1970	4.2	2.4	1.4	2.5	3.7	4.3	1.2	2.3	1.1	extrapolation from \sum PCB intake (3 µg/day) ¹⁾
1982	0.8	0.3	0.2	0.7	1.4	1.8	0.4	0.9	0.3	MAFF (1996)
1990	1.1	0.7	0.4	0.5	0.6	0.7	0.2	0.4	0.2	Duarte-Davidson and Jones 1994
1992	0.2	0.1	0.1	0.1	0.3	0.3	0.1	0.2	0.1	MAFF (1996)
1997	0.2	0.2	0.2	0.5	1.0	1.0	0.3	0.5	na	MAFF (1999)
2001	0.2	0.1	0.1	0.3	0.6	0.8	0.1	0.3	0.2	FSA (2003)

1) Different estimates for \sum PCB intake in 1970 (Duarte-Davidson and Jones 1994; MAFF 1983) were multiplied by congener fractions from later studies (Duarte-Davidson and Jones 1994; MAFF (1996)); see text for details

2) Assuming a body weight (bw) of 70 kg

Empirical Cross-Sectional Data

We use two empirical age/concentration CSD from the general UK population sampled in 1990 (Duarte-Davidson et al. 1994) and in 2003 (Thomas et al. 2006). Duarte-Davidson (1994) reported that they found no statistically significant differences between log \sum PCB in males and female individuals. Thomas et al. (2006) reported significant differences in the age/concentration relationship between males and females only for higher-chlorinated PCB congeners based on an analysis using linear regression. However, the age/concentration relationship is not linear over the whole age range. As a consequence, results from linear regressions over the whole age range are likely to be biased, in particular, because there were more female than male individuals older than 70 years in the data set. No significant correlations between concentration of PCBs in females in relation to number of children carried (or breast fed) were found (Thomas et al. 2006). In summary, effects of gender and parity have been found to be small in the data sets used in this study.

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